DETAILED ACTION

Response to Amendments/Arguments

No amendments were made to the claims. Claims 1-10, 12-15 and 21 are canceled. Claims 11, 16-20 and 22-35 are pending.

Applicant's arguments filed July 22, 2009 have been fully considered but they are not persuasive.

Applicant's state that since the prior office action stated that the previous rejections were maintained, both office actions mailed on November 2, 2007 and January 22, 2009 will be addressed. The Examiner inadvertently indicated in the previous office action that the office action of November 2, 2007 was maintained, however, said rejections were modified to better clarify the prima facie case of obviousness, and as such the body of the rejection and some of the references were changed. Applicant's arguments regarding the previous office action mailed on November 2, 2007 were either previously addressed in the last office action or no longer apply as a modified rejection for better clarification was made on January 22, 2009. As such, only newly presented arguments in response to the office action sent out on January 22, 2009 will be addressed in this response.

Applicants argue that synergism in the periphery would not be expected based on synergism for systemically administered drugs because even if synergism for systemically administered drugs were known, synergism for topically administered drugs was not known at the time the invention was made and would not have been

predictable. Furthermore Applicants argue that when acting centrally, drugs can have many possible locations to act, however, in the periphery, it is necessary for two drugs to act on the same axon to have a synergistic effect.

These arguments are found not persuasive since Elkhoury et al. teach that topical administration of morphine produces analgesia in the periphery and Elden et al. teach that butamben is a known local analgesic which acts in the periphery. Therefore it would be obvious to combine two drugs useful for the same purpose in order to achieve an increased effect. Although, Saito et al. teach that morphine combined with a similar local anesthetic (lidocaine) with the same mechanism of action as butamben, produce synergistic effects systemically, in the absence of unexpected results, an ordinary skilled artisan would reasonably expect that the combination would also produce synergism when combined in the periphery since butamben is a known local anesthetic with action in the periphery that is applied topically and morphine induces analgesia either systemically or peripherally by binding to opioid receptors in the brain or in peripheral tissues to induce analgesia and furthermore butamben and morphine have different mechanisms of action from each other and synergistic interactions are more likely when drugs act on different mechanisms.

Applicants argue that the office action relies upon post published art (Kolesnikov et al.). However, Kolesnikov et al. was not relied upon in the previous rejections. Kolesnikov et al. was introduced by Applicants in the declaration filed on May 1, 2006 by Yuri Kolesnikov and Gavril Pasternak. Kolesnikov et al. was addressed in response to Applicant's declaration and was not intended to apply as prior art. However, since

Applicants introduced Kolesnikov et al. it was pointed out that Kolesnikov et al. conclude that the synergistic effects of topical lidocaine and morphine were not unexpected and that synergistic interactions are more likely when drugs act on different mechanisms, as shown between morphine and butamben (see page 1107). Thus there is a reasonable expectation of success that when butamben is administered topically with morphine, a synergistic effect would occur and therefore the synergistic results as claimed in the instant application is not unexpected.

Applicants argue that topical combination of morphine and butamben in the periphery produces a synergistic result that would have been unexpected since prior to the teachings of the instant application, peripheral mechanisms in the mediation of antinociceptive responses were unknown. Applicants further argue that opioid analgesia was largely perceived to be mediated through the central nervous system (systemically) and not through opioid receptors located at peripheral sites and that those skilled in the art did not appreciate the significance of opioid stimulation at peripheral sites, much less the significance of combining opioid analgesics and local anesthetic at these peripheral sites. Applicants have also provided several references teaching that the topical use of morphine fail to stimulate peripheral sites.

These arguments are found not persuasive since the prior art reference, Elkhoury et al. teach that opioid analgesia is mediated through opioid receptors located at peripheral sites. Elkhoury et al. teach the topical application of opioid analgesic drugs such as morphine in diluted solutions to produce an analgesic effect in a localized area and without a transdermal migration of the opioid drug into the blood stream (see

abstract). Elkhoury et al. further teach that even prior to said invention it was discovered that opioid receptors are also located in other peripheral tissues and that antinociceptive effects of mu- and kappa-agonists in inflammation are enhanced by a peripheral opioid receptor-specific mechanism of action (see column 2 lines 3-26). Elkhoury et al. further teach that a large number of animal studies were performed to characterize peripheral opioid receptors and their activation by morphine and other opioid drugs and that a most important determination from these studies revealed that the doses of drugs required to produce analgesia in the peripheral tissues were extremely small and therefore devoid of side effects produced by dosages sufficient to operate on the brain (see column 2 lines 12-26). Thus Elkhoury et al. teach that peripheral analgesia of morphine was known at the time of the instant invention.

Applicants further argue that the declaration by Sandra C. Roerig filed on August 16, 2007 providing evidence of the state of the art at the time of the instant invention was not discussed in the previous office action except to state that it was found not persuasive. The declaration states that topical administration of morphine and lidocaine produced an unexpected synergistic antinociceptive response in the periphery and that studies of this kind had never been performed. This declaration is found not persuasive because it lacks any further explanation. No data or explanation was presented to support the conclusions stated. Furthermore the declaration does not mention the action in the periphery as compared to systemic action. Thus as stated above, since Saito et al. teach that morphine combined with a similar local anesthetic (lidocaine) with the same mechanism of action as butamben, produce synergistic effects systemically,

in the absence of unexpected results, an ordinary skilled artisan would reasonably expect that the combination would also produce synergism when combined in the periphery.

Furthermore as pointed out in the previous office action, which was not addressed by the Applicants, Applicants data with regard to synergism between topical administration of butamben and morphine are not commensurate in scope with Applicants claimed invention. Claim 11 of the instant application claim synergistically effective amounts of morphine and butamben without providing specific doses of each drug. Claims 16-20 and 22-26 claim wide ranges of morphine and butamben concentrations. However, the data provided by Applicants in the declaration filed on May 1, 2006 show that the administration of morphine and butamben applied locally produce a synergistic effect when the combination is applied at a fixed ratio of 1:0.4 of morphine to butamben.

Claims 27-32 were rejected under 35 USC 103 as described above and further in view of Mayer et al. Claims 34-35 were also rejected under 35 USC 103 as described above and further in view of Soo. Applicants only argue that the combination of Mayer et al. or Soo do not remedy the deficiencies of Elkhoury et al. and Elden et al. in view of Saito et al. and Goodman and Gilman. This argument is found not persuasive as discussed above.

For the reasons set forth above and for the reasons of record the prior rejections of January 22, 2009 under 35 USC 103 are hereby maintained, and reproduced below.

This action is made **final**.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 11, 16-20, 22-26 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Elkhoury et al. U.S. Patent No. 5,589,480 (provided on IDS) in view

of Elden U.S. Patent No. 5,814,659 and further in view Saito et al. (1998, Anesthesiology, Volume 89(6), pages 1455-1463-provided on IDS) and Goodman and Gilman (The Pharmacological Basis of Therapeutics, seventh edition, pages 302-305 and 310-312).

Claims 11, 16-20, 22-26 and 33 of the instant application claim a method of providing topical analgesia comprising administering to peripheral sites synergistically effective amount of morphine and butamben.

Elkhoury et al. teach the topical administration of an opioid drug, such as morphine, to produce an analgesic effect in a localized peripheral area and without a transdermal migration of the opioid drug into the blood stream (see Abstract). Elkhoury et al. further teach that it has been determined in the present invention that extremely small systemically inactive doses of both conventional opioid drugs such as morphine and other opioids can produce potent analgesic effects after local application in peripheral tissue (see column 2, lines 55-60). Elkhoury et al. further teach that the opioid may be applied using a variety of different topical formulations such as sprays, gels, creams, etc. and can be applied to the skin to relieve pain without the typical side effects associated with oral or injectable narcotics (see column 4, lines 46-57). Elkhoury et al. teach in column 5 lines 5-13 a specific example of a morphine spray wherein 90 mg of morphine is provided in a total of 129 ml of saline solution which is equivalent to approximately 0.07% of morphine provided in the solution.

Elkhoury et al. do not teach the inclusion of butamben and thus a synergistic combination.

Elden teaches topical analgesic compositions and methods for inducing topical analgesia (see abstract). Elden teaches compositions comprising an analgesic agent such as butamben picrate (see column 2 lines 14-18). Elden further teaches that the method of providing topical analgesia comprises bringing the topical analgesic composition (for example applied to a cotton strip or inserted into a typical skin-wipe packet) in contact with the skin of a person in need of such analgesia and maintaining the composition in contact with the skin for a period of time sufficient to induce and maintain topical analgesia (see column 3 lines 3-11). Elden further teaches a number of topical agents are known in the art such as butamben picrate and that the analgesic agent typically comprises from about 0.2 to 20 % by weight of the final composition (column 3 lines 27-34). Furthermore, claims 1-2 of Elden claim a topical analgesic composition comprising from about 0.2 to about 20 weight percent of an agent selected from benzocaine, butamben picrate, lidocaine, etc.

Accordingly, one of ordinary skill in the art at the time of the instant invention would have found it obvious to combine the teachings of Elkhoury et al., which teach topical analgesic compositions comprising morphine and other opioids for the treatment of pain, with the teachings of Elden, which teach topical analgesic compositions comprising butamben for the relief of pain. Thus, since both morphine and butamben are both topical analgesics useful for local administration for the relief of pain, one of ordinary skill in the art would be motivated to combine morphine and butamben in a composition with a reasonable expectation of success in providing an improved treatment of localized pain upon local administration of the composition. "It is prima

facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose ....[T]he idea of combining them flows logically from their having been individually taught in the prior art." In re Kerkhoven, 626 F.2d 846, 850,205 USPQ 1069, 1072 (CCPA 1980).

One of ordinary skill in the art would also be motivated to combine the morphine and butamben in a composition based on the concentrations taught in the prior art references (0.07% of morphine (Elkhoury et al.) and between 0.2%-20% of butamben (Elden)). Elkhoury et al. and Elden teach overlapping ranges of concentrations of morphine and butamben as claimed in claims 16, 17, 19, 20 and 22-25 of the instant application. Thus since the composition of morphine and butamben is rendered obvious it would also be obvious to one of ordinary skill in the art that the combination would produce a synergistic effect since it is obvious to combine the compounds in similar concentrations as claimed in the instant application (as taught by Elkhoury et al. and Elden). A compound and its properties are inseparable. In re Papesch, 315 F.2d 381, 137 USPQ 43 (CCPA 1963).

Elkhoury et al. and Elden do not teach concentrations of morphine as claimed in claim 18 of the instant application and concentrations of butamben as claimed in claim 26 of the instant application. However, it would be within the skill of an ordinary skilled artisan to modify the concentrations of the drugs within the composition based upon the effect desired. It has been held that it is within the skill in the art to select optimal parameters, such as amounts of ingredients, in a composition in order to achieve a

beneficial effect. See In re Boesch, 205 USPQ 215 (CCPA 1980). Furthermore, it is obvious to vary and/or optimize the amount of a compound provided in the composition, to provide a composition having the desired properties such as the desired (ratios, concentrations, percentages, etc.). It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

Furthermore the teachings of Saito et al. in view of Goodman and Gilman render obvious the synergistic combination of morphine and butamben. Saito et al. teach, on page 9, that morphine and lidocaine have a synergistic antinociceptive interaction in both bolus injections and in continuous coinfusion in which the agents are administered in small volumes and low concentrations. Further Saito et al. notes that in a recent study it was shown that morphine and bupivacaine induced a faster onset and a modest hypoalgesic effect than when administered separately. On page 10, Saito et al., teach that different opioid receptor subtypes have different characteristics and demonstrate different antinociceptive effects; further individual local anesthetics have different features, such as potency, duration, and motor block. Thus different opioid sub-types can have differing mechanisms of action, whereas the local anesthetics (like lidocaine and bupivacaine) have the same mechanism of action but differ in their pharmacological properties.

Goodman and Gilman teach, on pages 302-303 that local anesthetics have many actions in common and their primary mechanism of action involves a block of

conduction by decreasing the large transient increase in the permeability of the membrane to sodium ions that is produced by a slight depolarization of the membrane. On page 310 the pharmacological action of lidocaine and procaine are as previously detailed (see above mechanism of action). On page 312 Goodman and Gilman detail two local anesthetics with low aqueous solubility, namely benzocaine (structurally identical to procaine without the terminal diethylamino group) and butamben picrate. It is taught that these compounds can be applied directly to wounds and ulcerated surfaces as their poor solubility makes their systemic absorption too slow to be toxic. Further when applied they remain localized for long periods of time to produce a sustained anesthetic action.

It would have been obvious to one of ordinary skill in the art that the combination of butamben and morphine would result in a synergistic effect since Saito et al. teach that it is known that administration of morphine with lidocaine results in a synergistic antinociceptive effect and Goodman and Gilman demonstrate that local anesthetics such as lidocaine and butamben have the same mechanism of action (sodium ion effect). One of ordinary skill in the art would have expected that butamben would posses synergistic activity with morphine as butamben's mechanism of action is the same as lidocaine and further as Saito et al. point out that synergistic activity has been seen with another local anesthetic (bupivacaine) in conjunction with morphine. Although Saito et al. teaches synergistic effects upon systemic administration, an ordinary skilled artisan would also expect the same synergistic effect when administered peripherally since the combination is able to produce a synergistic effect systemically

and it is known that morphine induces analgesia either systemically or peripherally by binding to opioid receptors in the brain or in peripheral tissues to induce analgesia. Furthermore, since butamben and morphine have different mechanisms of action from each other it is likely that the combination would be greater than additive and likely synergistic.

Claims 27-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Elkhoury et al. U.S. Patent No. 5,589,480 (provided on IDS) in view of Elden U.S. Patent No. 5,814,659 and further in view Saito et al. (1998, Anesthesiology, Volume 89(6), pages 1455-1463-provided on IDS) and Goodman and Gilman (The Pharmacological Basis of Therapeutics, seventh edition, pages 302-305 and 310-312) as applied to claims 11, 16-20, 22-26 and 33 above, and further in view of Mayer et al. U.S. Patent No. 5,840,731.

Elkhoury et al. in view of Elden and further in view Saito et al. and Goodman and Gilman is as set forth above

The recited references lack a teaching of an NMDA receptor antagonist.

Mayer et al. teach that the analgesic effectiveness of a combination drug composition comprising at least one analgesic is significantly enhanced by the addition of an NMDA receptor antagonist (see Abstract). Mayer et al. teach compositions comprising a first analgesic, a second component, and an analgesia-enhancing amount of an NMDA receptor antagonist and methods of treatment for alleviating pain by the administration thereof (column 1, lines 6-27; column 2, lines 30 to column 3, line 5;

column 4, line 67 to column 5, line 13). Analgesics are taught to be selected from morphine, fentanyl, etc. (column 3, lines 57-65). NMDA receptor antagonists are taught to be selected from dextromethorphan, dextrophan, ketamine, memantine, pyrroloquinoline quinone, and cis-4-(phosphonomethyl)-2-piperidinecarboxlic acid (column 4, lines 33-50). Further, claims 1 and 2 of Mayer et al. claim methods and compositions for alleviating pain comprising a composition comprising an analgesic (e.g. morphine), a non-opioid analgesic, and a nontoxic NMDA receptor antagonist (e.g. dextromethorphan).

Mayer et al. further teach the amount of the nontoxic NMDA receptor antagonist will be at least that which is required to significantly enhance the analgesic effectiveness of the analgesics present in the dose and that suitable amounts of the antagonist can readily be determined by employing routine procedures (see column 4 lines 55-61). Generally the amounts of the antagonists can vary from about 10 to about 100 and preferably from about 15 to about 60 mg per unit dose (see column 4 lines 61-65). Examples 1-26 in columns 6 and 7 teach specific examples of compositions comprising 30 mg of dextromethorphan as the NMDA receptor antagonist which is approximately 4% or more of the total composition.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to administer a topical composition comprising the morphine, butamben and an NMDA receptor antagonist because (1) Elkhoury et al. and Elden teach the morphine and butamben, respectively, as analgesics suitable for topical administration; and (2) Mayer et al. teach that the addition of an NMDA receptor

antagonist (e.g. ketamine) to an analgesic composition is known in the art to significantly enhance the analgesia provided thereby. One of ordinary skill in the art would have been motivated to prepare and utilize such a composition because of an expectation of success in providing a topical composition suitable for peripheral relief with significantly enhanced analgesic effects, as taught by Mayer et al.

It is noted that Mayer et al. teach the NMDA receptor antagonists disclosed therein for achieving improved analgesia generally. Mayer et al. specifically teach amounts of NMDA receptor antagonists of about 4% or greater. Although Mayer et al. does not specifically teach lower concentrations as claimed in claims 31 and 32 of the instant application, Mayer et al. teach that the amount of the nontoxic NMDA receptor antagonist will be at least that which is required to significantly enhance the analgesic effectiveness of the analgesics present in the dose and that suitable amounts of the antagonist can readily be determined by employing routine procedures. Accordingly, it has been held that it is within the skill in the art to select optimal parameters, such as amounts of ingredients, in a composition in order to achieve a beneficial effect. See In re Boesch, 205 USPQ 215 (CCPA 1980). Furthermore, it is obvious to vary and/or optimize the amount of a compound provided in the composition, to provide a composition having the desired properties such as the desired (ratios, concentrations, percentages, etc.). It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

Claims 34-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Elkhoury et al. U.S. Patent No. 5,589,480 (provided on IDS) in view of Elden U.S. Patent No. 5,814,659 and further in view Saito et al. (1998, Anesthesiology, Volume 89(6), pages 1455-1463-provided on IDS) and Goodman and Gilman (The Pharmacological Basis of Therapeutics, seventh edition, pages 302-305 and 310-312) as applied to claims 11, 16-20, 22-26 and 33 above, and further in view of Soo U.S. Patent No. 5,028,595.

Elkhoury et al. in view of Elden and further in view Saito et al. and Goodman and Gilman is as set forth above. Furthermore, it is noted that Elkhoury et al. specifically teach the treatment of painful conditions associated with inflammation (column 2, lines 51-60).

The recited prior art references do not specifically disclose the treatment of acute and chronic peripheral neuropathy and neuropathic inflammation.

Soo teaches that morphine is known in the art for the treatment of peripheral neuropathy (column 1 lines 62-66).

It would have been obvious to one of ordinary skill in the art at the time of the invention to treat the claimed conditions because (1) Elkhoury et al. teaches that morphine is known in the art to treat painful inflammatory disorders in general; and (2) Soo teaches that morphine is known in the art to treat peripheral neuropathy. One would have been motivated to treat the claimed conditions with the morphine

compositions of the invention because of an expectation of success in treating the pain associated with the conditions.

Conclusions

Claims 1-10, 12-15, and 21 are canceled. Claims 11, 16-20, and 22-35 are rejected. No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KARA R. MCMILLIAN whose telephone number is (571)270-5236. The examiner can normally be reached on Monday-Thursday from 8:30 am- 6:00 pm and every other Friday from 8:30 am- 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571)272-0629. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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